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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)	
20052/1200522-US1	

Application Number	Filed
09/835,126-Conf. #4674	April 16, 2001

First Named Inventor: Randolph J. Noelle et al.

Art Unit	Examiner
1644	P. Gambel

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant /inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

☒ attorney or agent of record.
Registration number 57,895

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34. _____

Signature

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Typed or printed name

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Telephone number

June 30, 2006
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of 1 forms are submitted.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:

Randolph J. NOELLE

Application No.: 09/835,126 Art Unit: 1644

Filed: April 16, 2001 Examiner: P. Gambel

For: EX VIVO TREATMENT OF ALLOGENEIC AND XENOGENEIC DONOR T-CELLS CONTAINING COMPOSITIONS (BONE MARROW) USING gp39 ANTAGONISTS AND USE THEREOF

PRE-APPEAL BRIEF REQUEST FOR REVIEW

MS AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Concurrent with the filing of a Notice of Appeal, and in accordance with the Pre-Appeal Brief Conference Program, Applicants hereby request a pre-Appeal Brief review of the final rejection mailed April 11, 2006 in the above-identified application. No amendments are being filed with this request. With all claims having been twice rejected, an appeal is proper in accordance with 37 C.F.R. § 41.31(a).

Claims 1, 2, 4-7, 10, 11 and 13 are pending in the application. The sole questions on appeal are whether the Examiner is correct in rejecting (a) claims 1, 2, 4-11 and 13 under § 112, paragraph 1, for lack of written description; and (b) claims 1, 2, 4-11 and 13 under 35 U.S.C. § 103(a) as allegedly obvious over **Noelle** (U.S. Patent No. 5,876,718), in view of **Rooney** et al. (U.S. Patent No. 5,962,318), and in view of **Riddell** et al. (J. Immunol. Methods 128: 189-201) and **Sykes** et al. (U.S. Patent No. 6,006,752), and in further view of **Ochoa** et al. (Ochoa) (U.S. Patent No. 5,725,855) and **Knulst** et al. (Knulst) (Eur. J. Immunol. 23: 299-302, 1993).

Review is being requested for the following reasons:

The present invention provides a successful method for treating donor T-cells *ex vivo*, to render such T-cells substantially non-responsive to recipient antigens. The specification of this application describes a method for treating donor T-cells *ex vivo* with a gp39 (CD154) antagonist and recipient cells.

The method called for in the present claims renders donor T-cells substantially non-responsive to recipient antigens. The claimed method thus provides an effective means of preventing or inhibiting Graft Versus Host Disease ("GVHD") responses that would otherwise potentially occur upon transplantation of donor tissues into a recipient.

The inventors were the first to determine that the GVHD response can be controlled by tolerizing donor T-cells *ex vivo* in a specific manner prior to transplantation. First, CD4+ helper T-cells are removed and purified from the donor; as an additional requirement, recipient cells are irradiated to remove recipient T-cells; then the purified T-cells are incubated in a mixed lymphocyte reaction culture with the irradiated recipient cells and a gp39 antagonist. Exposure to the recipient cells in combination with the gp39 antagonist causes any donor CD4+ T-cells that recognize the recipient cells as foreign to become inactive. When treated in this manner, transplanted tissue does not cause a GVHD reaction in tissue transplant recipients.

The Rejection under 35 U.S.C. § 112, paragraph 1, should be withdrawn:

The Examiner contends that the specification does not provide support for claim 1, steps (i) and (iii)-(vi), or for the time ranges recited in claims 6 and 7 of "about 5 to 30 days" and "6 to 10 days."

Support for the rejected claim terms is specifically set forth in the specification (*see* Response dated February 28, 2006, pages 7-8). Further, with regard to claims 6 and 7, the time ranges recited in these claims is supported by the specification at page 8, lines 28-29, which recites "[t]ypically, this time will range from about 1-2 days to 30 days, more typically about 5-15 days, and most typically about 10 days" (emphasis added). Those skilled in the art would easily recognize that the inventors were in possession of the disputed claim limitations.

Thus, claims 1, 2, 4-11 and 13 are fully described in the specification and the rejection of the claims under 35 U.S.C. § 112, paragraph 1, should be withdrawn.

The Rejection under 35 U.S.C. § 103 should be withdrawn:

The Examiner concedes that **Noelle**, the primary reference relied upon by the Examiner, does not teach: (1) the purification and (2) testing of isolated CD4+ T-cells in a (3) mixed lymphocyte reaction (MLR) under the claimed conditions. Nonetheless, the Examiner argues that **Rooney**, **Riddell**, **Sykes**, **Ochoa**, or **Knulst** provide these missing limitations and would have been combined with **Noelle** by one of ordinary skill in the art at the time of the invention with a reasonable expectation of success of achieving Applicants' claimed invention (*see* Office Action dated December 30, 2005, page 4).

Applicants submit that the Examiner has failed to present a case of *prima facie* obviousness based on the cited references (*see* Response dated February 28, 2006, pages 8-20). Three basic criteria must be

met to establish a *prima facie* case of obviousness: (1) the references taken alone or in combination must teach or suggest all the claimed limitations; (2) suggestion/motivation in the references or in the general knowledge of one having ordinary skill in the art to modify or combine reference teachings; and (3) a reasonable expectation of success (MPEP § 2143).

(1) All the claimed limitations are not taught or suggested by the references taken alone or in combination

Steps: (i) "purifying CD4+ T-cells from donor tissue"; and (ii) "irradiating alloantigen-bearing cells obtained from a recipient to deplete recipient T-cells" of claim 1 are not taught or suggested by any of the cited references, either alone, or in combination. Further, absent the limitations recited in claim 1 steps (i) and (ii), the specific MLR recited in claim 1 steps (iii)-(v) and comprised of the cells as defined in steps (i) and (ii), is also not rendered obvious (*see* Response dated February 28, 2006, pages 12-16).[1]

With regard to the claim limitation of "purifying CD4+ T-cells", the Examiner concedes that **Noelle** does not teach the purification of CD4+ T-cells (*see* Office Action dated December 30, 2005, page 4). **Knulst** also does not teach or suggest *ex vivo* modification of donor cells, and, thus, does not teach or suggest "purifying CD4+ T-cells from donor tissue" in the context of claim 1 step (i), or the MLR of step (iii). **Rooney**, **Ochoa**, **Riddell**, and **Sykes** are completely silent as to "purifying CD4+ T-cells from donor tissue".

With regard to the claim limitation of "irradiating alloantigen-bearing cells obtained from a recipient to deplete recipient T-cells", **Noelle**, **Rooney**, **Ochoa**, and **Sykes** do not teach or suggest the use of irradiation to deplete only T-cells from a population of alloantigen-bearing cells. **Noelle** merely suggests that T-cells can be depleted by treatment with anti-T-cell antibody (Noelle, col. 10, ll. 34-37). **Rooney** teaches irradiation to deplete alloantigen-bearing cells (including mononuclear phagocytes, dendritic cells, and B cells) generally (*see* Rooney at col. 14, l. 57 - col. 15, l. 5; col. 10, l. 66 - col. 11, l. 2). **Ochoa** teaches other methods to create a "depleted immune cell population and immune cell subsets, [that] preferably develop increased immunotherapeutic activity" (Ochoa, col. 9, ll. 19-22), including the use of magnetic beads (Examples 1 and 3), a centrifuge (Example 2), irradiation of CD4+ and CD8+ T-cells isolated from culture (Example 5), and a cell purification column (Examples 6, 7, 10 and 11). **Sykes**, like Noelle, teaches that anti-T-cell antibodies lead to T-cell depletion (Sykes, col. 10, ll. 25-27). **Riddell** and **Knulst** are wholly silent on the issue of irradiation to select subpopulations of cells.

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[1] Claims 2, 4-7, 10, 11 and 13 all depend from claim 1 and thus contain every limitation of claim 1. These claims are not obvious for the same reasons set forth for claim 1.

Because the limitations of claim 1 steps (i) and (ii) are not taught or suggested by the prior art, either taken alone, or in combination, the specific MLR comprised of purified CD4+ donor T-cells and irradiated T-cell depleted alloantigen-bearing recipient cells recited in claim 1 steps (iii)-(v) is also not taught or suggested by the cited references. Accordingly, the particular MLR that is maintained in claim 1 step (v), in culture for a sufficient time to render the donor CD4+ T-cells substantially tolerant or non-responsive to the irradiated T-cell depleted alloantigen-bearing recipient cells, is also not taught or suggested by the cited references. Accordingly, because the limitations in claim 1 steps (i) and (ii) are not suggested or disclosed within the cited prior art, claim 1 is not obvious.

(2) There is no suggestion or motivation in the references or in the general knowledge of one having ordinary skill in the art to modify or combine the reference teachings

The Examiner underestimates the unpredictability in this art. He improperly and wrongly presumes that one of ordinary skill in the art at the time of the invention would have considered the gp39 pathway as a simple on/off switch and, thus, would just as soon turn to references teaching its activation as its deactivation. To this end, the Examiner concedes **Rooney** and **Riddell** (like **Ochoa**) may use T-cells to accomplish different endpoints, i.e., enhanced vs. tolerized immune response (Office Action, dated December 30, 2005, page 6, paragraphs 4 and 8). Indeed, three of the cited references, **Rooney**, **Riddell**, and **Ochoa**, teach away from the claimed invention in that they disclose methods leading to *enhanced activation* of the immune system—an opposite result to immunotolerance (*see* Response dated February 28, 2006, pages 17-19).

Contrary to the induced immunotolerance of the presently claimed invention, **Rooney** seeks to *stimulate* an immune response to specific antigens for adoptive transfer, which is useful to treat infections in immunocompromised individuals, or to treat tumors (Amendment, dated June 21, 2005, pages 11-12, paragraphs 4-1; Rooney, cols. 14-15, paragraphs 4-1; *see* Rooney, Abstract, stating that "[t]he present invention is directed to methods of *stimulating* primary and secondary effector cell responses for cellular immunotherapy"). The Examiner acknowledges that **Riddell** similarly teaches "*expanding* human antigen-specific T-cells" (Office Action dated December, 30 2005, page 4, paragraph 5). The **Ochoa** reference teaches *enhancement* of an immune response such that "populations rapidly develop and maintain high levels of NK [natural killer] and LAK [lymphokine activated killer] activity" (Ochoa, col. 17, ll. 21-22).

It is understood that "a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant" (*Tec Air, Inc. v. Denso Mfg. Mich., Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999) (citing *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)); *see also In re Lundsford*, 148 U.S.P.Q. 721, 726 (CCPA 1966) (stating

that a reference which teaches an opposite concept teaches away, and cannot be properly combined to make an obviousness rejection)).

Thus, not only would one of ordinary skill in the art at the time of invention not have relied on these references, these references, in fact, teach away from the claimed method because they disclose methods producing opposite results in a highly unpredictable art. Indeed, Applicants submit that the *growth and expansion of antigen-specific T-cells is the central problem in GVHD for which the present invention can be used to circumvent*. Accordingly, the cited references would not suggest or motivate one of ordinary skill in the art to modify or combine the reference teachings.

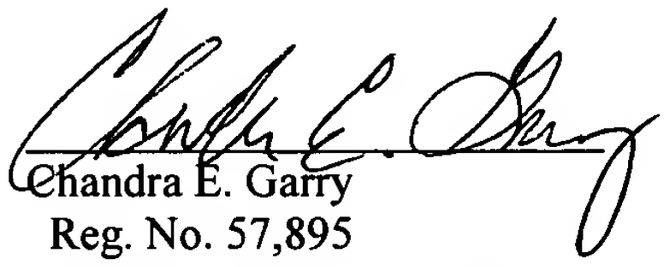
(3) The cited prior art and the knowledge of one of ordinary skill in the art do not give rise to a reasonable expectation of success

Even assuming arguendo that the cited references are properly cited and combined, the Examiner has presented a combination of references that provide no reasonable expectation of success for achieving the claimed invention as they do not account for all the claimed limitations and, in fact, teach away from the result of induced immunotolerance as presently claimed (*see* Response dated February 28, 2006, pages 19-20). Thus, one of ordinary skill in the art at the time of invention would not have been prompted by any combination of the cited prior art and/or their own knowledge to create the claimed method using an MLR comprising purified donor CD4+ T-cells, irradiated, T-cell depleted recipient alloantigen-bearing cells, and a gp39 antagonist to induce immunotolerance or non-responsiveness in the donor CD4+ T-cells.

For the reasons demonstrated above, the case should be returned to the examiner with an indication that the application is allowable.

Dated: June 30, 2006

Respectfully submitted,



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